

Botulinum Neurotoxins Summary

Introduction

Botulism is a potentially life-threatening clinical syndrome of descending cranial nerve and neuromuscular paralysis which is caused by a group of neurotoxins, serotypes A through G, produced by the bacterium *Clostridium botulinum*, and rarely by strains of *Clostridium baratii* and *Clostridium butyricum*. These are among the most potent toxins known, with an estimated human lethal dose of 0.01 micrograms per kilogram of body weight by the inhalation route, and 1.0 micrograms per kilogram orally. Endemic botulinum intoxication occurs in three main forms: food borne botulism, infant botulism, and wound botulism. In a bioterrorism attack, the routes of exposure would most likely be either oral or by inhalation. All botulism results from absorption of toxin into the circulation from a mucosal surface (GI mucosa or pulmonary epithelium) or from a wound. The toxin does not penetrate intact skin. Botulinum intoxication is not contagious and person-to-person spread does not occur.

Toxicity varies somewhat according to serotype, with type A typically causing more severe disease, and types B and E generally causing less severe disease. These toxins consist of a 100 KD heavy chain joined to a 50 KD light chain. The light chain is the active moiety, a Zn⁺⁺ containing peptidase, which prevents the release of acetylcholine from pre-synaptic motor and ganglionic neurons, producing a characteristic clinical picture of bulbar palsies and flaccid muscular paralysis leading to respiratory failure. Once neuronal cells take up toxin, clinical effects may be very long lasting (weeks to months).

State-sponsored biological programs have shown interest in botulinum toxins as weapons: prior to the 1991 Persian Gulf War, Iraq weaponized more botulinum toxin than any of its other BW agents – 19,000 liters of botulinum type A toxin, with approximately 10,000 liters loaded into military weapons. The technology for producing botulinum toxins is fairly crude – well within the reach of potential biological terrorists.

Types of Clinical Botulism

Food borne Botulism - occurs when humans ingest pre-formed botulinum toxin in contaminated foods. All ages and both genders are susceptible. This form of botulism is fairly uncommon, with an average incidence of 24 cases per year in the United States. Heating inactivates the toxin, thus cases are always associated with foods that are not heated or are inadequately cooked. Many types of food have been associated with outbreaks, but cases have occurred more often in the U.S. with low-acid (higher pH), improperly canned vegetables such as beans, carrots, corn, and peppers. Cases occur more often in the western U.S., in Alaska, California, Washington, Oregon, and Colorado; interestingly, type A intoxication is more common in the west and overall, and

type B cases are the predominant type in the eastern U.S. Most food borne outbreaks in Alaska and Canada are type E disease associated with native Eskimo and Inuit foods. Type F cases are rare, and type C and D outbreaks are limited to wildlife and domestic animals, but have not caused outbreaks in humans. Susceptibility in humans is assumed, however, from non-human primate studies. The food supply could be targeted in a bioterrorism attack with botulinum toxin, mimicking an endemic outbreak, but potentially much larger in terms of numbers of cases.

Infant Botulism - occurs when young infants ingest spores of *Clostridium botulinum*, most commonly in contaminated honey used to sweeten milk or on a pacifier. This is the most common type of botulinum intoxication in the U.S., causing nearly three-fourths of all botulism cases. The pathophysiology of infant botulism is different than that of food borne disease. Clostridial bacteria are able to survive in the infant gut, and may then produce toxin over time that is continually absorbed and causes symptoms. Affected infants exhibit poor feeding, constipation, floppiness, and failure to thrive; impaired respiratory function and death may occur in severe or untreated cases.

Wound Botulism – the least common clinical form of botulism in the U.S., causing less than 5% of cases. Usually occurs in young males with spore-contaminated open wounds. Spores of *C. botulinum* are ubiquitous in the environment and in soil. Clostridia produce toxin in the contaminated wound, which is absorbed into the circulation and causes the characteristic signs and symptoms of botulism.

Inhalation Botulism – does not occur naturally, but could occur in an aerosol bioterrorism attack using botulinum toxin. Botulinum toxins are rather unstable in the environment, thus the range of an aerosol attack may be limited. Cases might be clustered geographically at the time of exposure (building, work site, or focal ground location), without a common dietary exposure.

Clinical Picture

Botulism is an acute, symmetric, descending flaccid neuromuscular paralysis that always begins with cranial nerve (bulbar) palsies. Patients are afebrile, and most often present for care with difficulty speaking, swallowing, or with blurred or double vision. Mentation is preserved and sensation is not affected. Other signs and symptoms may include ptosis, dilated pupils, dysconjugate gaze, dry mouth, decreased gag reflex, hyporeflexia, paresthesia, arm or leg weakness, and occasionally, ataxia. In some cases, neurological signs and symptoms may be preceded by nausea, vomiting, abdominal cramping and diarrhea; these symptoms are thought to be due to co-ingestion of other non-clostridial bacteria or bacterial metabolites with the offending food. Constipation may also occur.

The progression of paralysis and its severity may vary considerably among patients, probably due to the amount of toxin consumed as well as individual host factors. Some patients may only need observation, while others may require intubation and prolonged (weeks or months) ventilatory support for respiratory failure. All should be hospitalized

and observed closely, as progression to respiratory failure may be rapid in some victims and is difficult to predict.

The incubation period between ingestion of the toxin and first signs of intoxication is usually 12 to 36 hours, and may be the same or possibly longer for inhalation cases, based on very limited animal data.

Epidemiologic Indicators

Sporadic endemic cases are recognized by the characteristic clinical picture, common dietary exposure to offending food or drink items in two or more affected individuals, and/or a history of risk factors for infant or wound botulism. Indicators of a bioterrorism attack may be: large numbers of cases exposed to a widely distributed commercial food item or common potential food source; an outbreak of botulinum intoxication cases with a common geographic factor but without a common dietary exposure (aerosol attack); multiple simultaneous outbreaks without a common source; an outbreak of intoxication caused by a toxin type unusual in humans (C, D, F, and G, or E not associated with an aquatic food).

Diagnosis and Treatment

Diagnosis: Clinical diagnosis: descending bulbar and symmetric flaccid paralysis

Diagnostic Samples: Serum or blood, gastric aspirate, feces, or food (specimens should be refrigerated).

Differential Diagnosis: Guillain-Barre Syndrome (Miller-Fisher variant), Myasthenia Gravis, Eaton-Lambert Syndrome, Tick Paralysis

Isolation/Decontamination Precautions: Standard Precautions

Treatment

- Intensive Supportive Care
- Antitoxins:
 - 1) Licensed Bivalent Anti-AB equine antitoxin, Aventis-Pasteur.
 - 2) IND Univalent Anti-E equine antitoxin, Aventis-Pasteur
 - 3) IND Heptavalent despeciated (Fab'2) equine Anti-ABCDEFG antitoxin, U.S. Army
 - 4) Licensed Anti-AB human antitoxin for infant botulism (HBIG – human botulinum immune globulin, sometimes referred to as “Baby-BIG”)

The first three products are available from CDC on a 24-hour basis. Local or state health departments should call CDC at 770-488-7100. After a clinical telephone consultation with a Foodborne and Diarrheal Disease branch physician, antitoxin will be immediately released if indicated.

HBIG for infant botulism is available from the California Department of Health Services, Infant Botulism Treatment and Prevention Program (Dr. Stephen Arnon) at 510-231-7600.

Case Scenarios – Botulinum Neurotoxins For CE Modules – Emergency Physician

Case 1 - Emergency Physician

During one Friday night 7 PM to 7AM 12-hour shift in your emergency department, you see four patients between the ages of 26 and 48, three adult males and one adult female, all of whom present over a two hour time period with various cranial nerve palsies to include diplopia, blurred vision, difficulty swallowing and speaking, and ptosis of the eyelids. There are no GI symptoms. Your careful history taking reveals that all of these patients work in the federal building downtown, which has been at high security recently due to the “level orange” terrorism alert. 600 people work in that building. All had lunch in the building dining facility yesterday and today, but only two patients apparently had common food exposures with a brief history. None of the patients appears to be in any respiratory distress, and there is as yet no evidence of peripheral weakness.

The most important action you can take is:

- A. Administer a food survey to try and better identify the likely vehicle of intoxication.
- B. Administer broad-spectrum antibiotics to all of the patients
- C. Order cranial MRI's on all four patients
- D. Immediately notify local and state public health authorities and the F.B.I. of your clinical suspicions
- E. Do a more complete neurological exam on each patient sequentially

(Answer – D)

Other important actions to take quickly include:

- A. Admit all four patients to the ICU for monitoring and possible supportive care
- B. Activate your hospital's disaster preparedness plans, and prepare for more victims
- C. Check with public health authorities on the early availability of antitoxin
- D. Call the on-call allergy and immunology specialist and tell him to prepare to come in
- E. A and C are correct
- F. A, B, C, and D are all correct

(Answer – F)

Case 2 – Emergency Physician

A nursing mother presents after hours to the Pediatric Emergency Department with her 3-month old male infant. She says that the baby had been doing well, but the past 48 hours has been feeding poorly, is irritable, and no longer seems to be able to hold his head up. The baby is nursing, with supplemental bottle feedings with the addition of honey that the mother buys from a local holistic food market. Your initial examination reveals a floppy baby with poor head control and flaccid facies with poor following and eye contact. The infant is afebrile.

Most important **initial** actions should include:

- A) IV access, cardiorespiratory monitoring, and arranging admission to the Pediatric ICU
- B) Notification of local public health authorities
- C) A phone call to the California Department of Health Services
- D) A sepsis work-up and the institution of age-appropriate antibiotic coverage
- E) A and D are correct

(Answer-E)

Following the above measures, the next most important actions are:

- A) Isolation of the infant from other patients
- B) A phone call to your hospital epidemiologist or infection control practitioner, asking him to contact the California Department of Health Services to request human antitoxin shipment
- C) A phone call to the CDC to request equine antitoxin shipment
- D) Notification of the baby's pediatrician of your suspected diagnosis
- E) B and D are correct

(Answer – E)

Case 3 – Emergency Physician

You receive a call during your shift from a colleague working at a small hospital Emergency Department in a small town about 30 miles from your city. She is concerned because of the presentation of several children from the local elementary school with signs and symptoms suggestive of botulism. She knows that you attended a CME course on medical management of biological casualties at USAMRIID at Fort Detrick, Maryland, last week. She asks you what factors would indicate an aerosol bio-terrorism attack as opposed to a natural food-borne outbreak of botulism. You correctly inform her that in the case of an aerosol bio-terrorism attack, she might expect:

- A) Presentation of many more suspected cases over the next few hours
- B) No common dietary exposure
- C) A common geographic factor in all cases
- D) No progression of symptoms since aerosol intoxication causes mild disease
- E) A and C are correct

(Answer - E)

After answering your colleague's question, you offer more correct information, which is likely pertinent to this case, based on what you learned at USAMRIID. You tell her:

- A) You believe that these cases could be due to an oral route of exposure and still be non-natural (bio-terrorism).
- B) You tell her that children are more susceptible to the effects of botulinum toxin than adults, which is probably why she is not seeing any adult cases.
- C) You ask her if all of the patients are males, since males are more susceptible to the effects of botulinum toxin.
- D) You discount the possibility that milk served in school lunches could be the vehicle of intoxication, as milk denatures botulinum toxin
- E) A and B are correct

(Answer – A)